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Variant: m.9537dupC

Version: 1.1

CA120602

9656 (ClinVar)

Gene: MT-CO3 (HGNC:4514)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 74807869-0714-43e3-b9c9-bb500bca4635
Approved on: 2024/4/22
Published on: 2024/12/11

HGVS expressions

NC_012920.1:m.9537dup
J01415.2:m.9537dup
ENST00000362079.2:c.331dup

Likely Pathogenic

Met criteria codes 3

PVS1_Strong PM2_Supporting PS3_Supporting

Not Met criteria codes 2

PP3 PS4

Evidence Links 2

Expert Panel

Mitochondrial Diseases VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Mitochondrial Diseases VCEP

The m.9537dupC variant in MT-CO3 has been reported in one individual with primary mitochondrial disease to date (PMID: 11063732), in an 11-year-old girl with Leigh syndrome spectrum disorder. Progressive spastic paraparesis, ophthalmoplegia, and moderate intellectual disability were noted at age four years, as was severe lactic acidosis and lesions in the putamina on brain imaging. The variant was reported as being “virtually homoplasmic” in skeletal muscle, fibroblasts, and lymphocytes. The variant was not detected in lymphocytes from her unaffected brother and maternal grandmother, and was similarly absent in lymphocytes, hair, and oral epithelial cells in her mother. However, technology at the time was limited in detecting low heteroplasmy levels. This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting). There are no in silico predictors for this type of variant in mitochondrial DNA. This frameshift variant at amino position 111 creates a stop codon three positions downstream, resulting in a significant (57%) truncation of the MT-CO3 protein (PVS1_strong). Cybrid studies supported the functional impact of this variant (PMID: 11063732), as did studies in colonic crypt stem cells (PMID: 14597761; PS3_supporting). In summary, this variant meets criteria to be classified as likely pathogenic for

primary mitochondrial disease inherited in a mitochondrial manner. This classification was approved by the NICHD/NINDS U24 ClinGen Mitochondrial Disease Variant Curation Expert Panel on April 22, 2024. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PVS1_strong, PM2_supporting, PS3_supporting.

Met criteria codes

PVS1_Strong	✔	The duplication at base position 9537 causes a frame-shift at codon 111, creating a STOP only 3 positions downstream. This causes a significant truncation (57%) of the CO3 protein.
PM2_Supporting	✔	This variant is absent in the GenBank dataset, Helix dataset, and gnomAD v3.1.2 (PM2_supporting).
PS3_Supporting	✔	100% mutant cybrid cell line showed a profound isolated COX defect (PMID 11063732).No full-length COX III protein was detected in these cells using in vivo mtDNA translation assays. Western blot analysis of 2D blue-native electrophoresis showed that the fully assembled COX complex was absent in the cybrids. Additionally, there was reduction of specific cross-reacting material and the accumulation of early-assembly intermediates of COX. In another study (PMID 14597761), colonic stem cells were used to demonstrate a COX deficiency in individual crypts carrying homoplasmic m,9537Cdup. Both COX complementation and biochemical assays using a 100% mutant cybrid cell line showed a profound isolated COX defect. No full-length COX III protein was detected in these cells using in vivo mtDNA translation assays. Western blot analysis of 2D blue-native electrophoresis showed that the fully assembled COX complex was absent in the cybrids. Additionally, there was reduction of specific cross-reacting material and the accumulation of early-assembly intermediates of COX. PubMed:11063732 Using colonic stem cells as a model system, this study showed COX deficiency in individual crypts carrying homoplasmic m,9537Cdup. PubMed:14597761

Not Met criteria codes

PP3	✖	No appropriate in-silico tools are currently available for prediction of pathogenicity for duplications or deletions.
PS4	✖	The MT-CO3 m.9537dupC variant has been reported in one patient, 11-year-old girl with a negative family history, with Leigh-like syndrome (Tiranti 2000 PMID 11063732). The homoplasmic variant m.9537dupC was found in both patient muscle and skin biopsy samples. It has also been reported in colonic crypt stem cells in a study of aging tissues (Taylor 2004 PMID 14597761).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	m.9537dupC	Likely Pathogenic	Mitochondrial Disease	2024-12-11	1.1	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	MT-CO3
View	m.9537dupC	Likely Pathogenic	Mitochondrial Disease	2024-12-11	1.0	ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA	N/A

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